REMARKS/ARGUMENTS

Claims 46-48, 50, 66-71, and 74 have been withdrawn from consideration pursuant to a restriction requirement. Claims 38-42, 44-50, 53-57, 59-60, 62-74 are pending. Claims 38, 42, 44-45, 49, 53-57, 59-60, 62-65, 72 and 73 are under consideration.

Citations to the Specification are directed to U.S. Patent Application Publication No. 2004/0265350 (Sambrook et al.).

Favorable reconsideration is respectfully requested in view of the following remarks.

Withdrawn Rejections

Applicant gratefully acknowledges the withdrawal of the following rejections: the rejection under 35 USC 112, second paragraph; the rejection under 35 U.S.C. 102(b) over Ishii (JP 04327525); the rejection of 35 U.S.C. 103(a) over Ishii (JP 04327525) in view of Itokazu; the rejection of 35 U.S.C. 103(a) as being unpatentable over Ishii (JP 04327525) in view of Laurencin (US 5,356,630); and the rejection of 35 U.S.C. 103(a) as being unpatentable over Ishii (JP 04327525) in view of Genin (US 6,767,550).

Rejection under 35 USC 103(a)

Claims 38-42, 44, 45, 53, 54, 59, 60, 62, 63, 72 and 73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (WO 98/15505), in view of Ishii (JP 04327525). This rejection is respectfully traversed.

The Examiner sets forth that Smith discloses porous ceramics infilled with drug substances for slow release, that the articles are preferably prepared from hydroxyapatite, and that pore sizes may range from 50 - 150 microns or greater than 150 microns.

The Examiner admits that Smith does not specifically recite that the drug located within the pores is present in a degradable support. However, the Examiner argues that Ishii discloses sustained release medicine-containing ceramic porous substances, and that the sustained release medicine-containing ceramic porous substances are capable of sustaining a medicine for a long period and preventing side effects due to concentrated elution of the medicine by applying a biodegradable substrate containing the medicine, dispersed and held therein to the inner wall surfaces in pores and on the outside surface of a ceramic porous substance (citing the ABSTRACT section of English Translation, and Figure 1). The Examiner further sets forth that

the biodegradable substrate containing the medicine is chitin and its derivative or collagen, and that calcium phosphate-based ceramics, particularly tricalcium phosphate and hydroxyapatite are especially preferred. Thus, the Examiner contends that Smith describes a carrier having pores made up of a network of coalesced spheres, and that Smith directs that its carrier could be filled with certain drugs such that it acts as a slow release agent at the site of an implant. The Examiner further argues that this teaching would be combined by the skilled person with the teaching of Ishii, such that he would place a drug in the pores of Smith's ceramic support in a degradable resin, thereby reaching the invention of claim 38 of the present application.

However, the claims are patentable over the combination of Smith (WO 98/15505), in view of Ishii (JP 04327525) for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

Here, Applicant submits that the invention as described in claim 1 of the present application is not obvious over Smith in view of Ishii. Claim 38 is drawn to a preformed porous ceramic carrier comprising an interconnected skeleton having pores the majority of which are in the range of from about 20 to about 800 micron, the carrier comprising block hydroxyapatite and having a density less than about 40% theoretical, the pores comprising a network of coalesced spheres the pores containing a second material deposited therein, the rate of release of the second material from the carrier being controlled by having the second material located within the pores in a degradable support.

Applicant, however, notes that Smith provides a direct method of producing ceramic porous articles (i.e. the method produces the porous structure intrinsically, rather than relying on a ready-made porous support) having a very broad range of potential porosities (20% to 95%) while only describing the potential use of the carrier therein described as a drug-filled implant in only the most cursory manner. No examples of how such a carrier might actually be filled with a drug, or demonstrations of how effective it may be, are provided in the Smith reference.

Ishii, on the other hand, provides that direct methods of manufacturing porous carriers are only effective for making carriers of less than 50% porosity (see Ishii at paragraph [0015]), while the greater porosity and control required for an effective drug release carrier can be provided only by the indirect method of saturating a polymer foam with ceramic slurry before burning the foam out and sintering the slurry (see Ishii at paragraph [0014]).

Applicant therefore submits that the skilled person would not be motivated to apply the teaching of Ishii to that of Smith, because Ishii teaches that direct methods of carrier production, as Smith describes, produce carriers unsuitable for drug delivery.

Even if the skilled person did apply the teaching of Ishii to that of Smith, the skilled artisan would make carriers of less than 50% porosity, the effective limit of porosity obtainable by direct manufacture of a carrier as noted by Ishii, whereas claim 38 explicitly requires a carrier of 60% porosity (40% density). Thus, the combination of Smith and Ishii do not teach or suggest all the limitations of Claim 38 of the instant application.

Applicant therefore submits that claim 38 is inventive over Smith in view of Ishii.

Claims 39 to 42, 44, 45, 53, 54, 59, 60, 62, 63, 72 and 73 are each directly or indirectly dependent upon either Claim 38. Applicant submits that these claims are also inventive over Smith in view of Ishii. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 103(a)

Claims 38-42, 44, 45, 53, 54, 59, 60, 62-65, 72 and 73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (WO 98/15505), in view of Ishii (JP 04327525), further in view of in view of Itokazu. This rejection is respectfully traversed.

The Examiner sets forth that Smith discloses porous ceramics infilled with drug

substances for slow release and Ishii discloses sustained release medicine containing ceramic porous substances containing a biodegradable substance which contains the medicine dispersed and held to the inner wall surfaces in pores and the outside surface of a ceramic porous substance, but admits that Smith and Ishii do not specifically teach that the anticancer drug is MTX. The Examiner alleges that Itokazu teaches porous apatite ceramics for the local delivery of chemotherapeutic agents.

The Examiner argues that the type of drug which is held includes antibiotics, anticancer drugs, protein drugs, an osteoplasty factor, etc. The Examiner argues regarding claims 42 and 59, the limitations "wherein the pores were formed by sintering a precursor of the carrier under conditions which were below those required for full sintering" or "wherein the second material is introduced into the pores by one or more of centrifugation, immersion, vacuum impregnation or freeze drying" appear to be a product-by-process type limitations, and that product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps.

The Examiner further argues regarding claims 72 and 73, wherein the ceramic carrier is shaped for orthopaedic maxillo-facial or cranio-facial replacement, etc. appear to be intended-use type limitations, because there are no limitations regarding the actual physical shape of the carrier. The Examiner argues that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Smith and Ishii and to provide the drug which is infilled in the microporous structure of Smith in a degradable support, such as collagen, chitin, etc. as in Ishii. The Examiner further argues that one would have been motivated to do so, and would have had a reasonable expectation of success in doing so because both Smith and Ishii are drawn to release of drugs from a porous hydroxyapatite ceramic (see Smith, pages 10-11; and Ishii, entire document), and because Ishii teaches that such a degradable support provides advantages such as distributed maintenance of drugs and maintaining continuous drug effect over time. Ishii also teaches the advantage of preventing side effects due to concentrated elution of the medicine by applying a biodegradable substrate containing the medicine, dispersed and held therein to the inner wall surfaces in pores and on the outside surface of a ceramic porous substance.

However, here claim 38 is drawn to a preformed porous ceramic carrier comprising an interconnected skeleton having pores the majority of which are in the range of from about 20 to about 800 micron, the carrier comprising block hydroxyapatite and having a density less than about 40% theoretical, the pores comprising a network of coalesced spheres the pores containing a second material deposited therein, the rate of release of the second material from the carrier being controlled by having the second material located within the pores in a degradable support. Claim 64 is drawn to a preformed porous ceramic carrier comprising an interconnected skeleton having pores the majority of which are in the range of from about 20 to about 1000 micron, the carrier having a density of less than about 40% theoretical, the pores comprising a network of coalesced spheres, the pores containing MTX, the rate of release of the MTX from the pores being controlled by having the MTX located within the pores in a degradable support.

Instant claim 38 requires a porous ceramic article having a density of 40% or less and pores comprising a network of coalesced spheres. Such an article, as discussed above, is not taught or suggested in the combination of Smith and Ishii. Smith provides a direct method of producing ceramic porous articles (i.e. the method produces the porous structure intrinsically, rather than relying on a ready-made porous support) having a very broad range of potential porosities (20% to 95%) while only describing the potential use of the carrier therein described as a drug-filled implant in only the most cursory manner. No examples of how such a carrier might actually be filled with a drug, or demonstrations of how effective it may be, are provided in the Smith reference. Ishii provides that direct methods of manufacturing porous carriers are only effective for making carriers of less than 50% porosity (see paragraph [0015]), while the greater porosity and control required for an effective drug release carrier can be provided only by the indirect method of saturating a polymer foam with ceramic slurry before burning the foam out and sintering the slurry (see paragraph [0014]).

In fact, Ishii actually teaches away from producing any article other than one having a tubular porosity, as it is stated in Ishii at ¶[0015] that articles produced by a method different to that of saturating a polyurethane sponge with a ceramic slurry and firing exhibit only up to 50% porosity.

Moreover, ¶[0014] of Ishii points out that pore sizes larger than 300 μm cause any drug

held within the porous article to be released too quickly. Once again, this teaches away from the invention recited in claim 38, which, in contrast, may have pores of up to 800 μm in diameter, and claim 64 which recites pores the majority of which are in the range of from about 20 to about 1000 micron. These larger pore sizes allow a greater quantity of drug to be held in each pore, while the join where two spheres have coalesced acts as a kind of throttle or collar to keep a drug held within the pores from leaching away quickly.

Additionally, the particular porous structure of the instantly claimed porous ceramic article helps to ensure that the pore network is totally interconnected, allowing for a far deeper fill (see ¶[0039] of the Application) than does the reticulated carrier of Ishii. This deficiency in Smith and Ishii teaching a porous ceramic carrier having a particular reticulated carrier porous configuration, as opposed to the totally interconnected pore network as claimed, is not remedied by Itokazu.

Itokazu does not provide any specific detail as to the configuration of the pores of the ceramic carriers noted. However, it is disclosed in the final paragraph of page 536 that the hydroxyapatite carrier used had pores between 50μm and 300μm in diameter, further reinforcing the teaching of Ishii. Itokazu does not, then, contain motivation for the skilled person to move away from the teaching or suggestions of the combination of Smith and Ishii to the larger pore sizes provided by the network of coalesced spheres of the invention recited in Claim 38 and 64. Claims 38 and 64, and the claims dependent therefrom, are therefore patentable over the combination of Smith in view of Ishii and further in view of Itokazu.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 103(a)

Claims 38-42, 44, 45, 53-55, 59, 60, 62, 63, 72 and 73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (WO 98/15505), in view of Ishii (JP 04327525), further in view of Laurencin (US 5,356,630). This rejection is respectfully traversed.

The Examiner sets forth that Smith discloses porous ceramics infilled with drug substances for slow release and Ishii discloses sustained release medicine containing ceramic porous substances containing a biodegradable substance which contains the medicine dispersed and held to the inner wall surfaces in pores and the outside surface of a ceramic porous

substance, as set forth above.

The Examiner admits that Ishii teaches collagen or chitin as a biodegradable support for the medicament, rather than PCPP-SA, as claimed, but argues that Laurencin discloses a system for the controlled or sustained release of bioactive substances which interact with local cell populations at a physiological site, and that the composition is formed of a bioerodable, surface-eroding polymer and the bioactive substance. The Examiner further argues that the "sustained" or "controlled" release of the substance may be either continuous or discontinuous (column 2, lines 20 - 26). Such bioerodable polymers are those which break down or disintegrate over time when placed in contact with biological fluids, and that examples of suitable polymers for such purposes include polyanhydrides such as a co-polymer of PCPP and sebacic acid (PCPP-SA).

The Examiner further argues that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute PCPP-SA as a functional equivalent for collagen as the biodegradable support which holds the medicament in the pores of the ceramic substance disclosed by Ishii.

However, the claims are patentable over the combination of Smith, Ishii and Laurencin for the following reasons. The claims are set forth above, and are not taught or suggested in the combination of Smith and Ishii. Smith provides a direct method of producing ceramic porous articles (i.e. the method produces the porous structure intrinsically, rather than relying on a ready-made porous support) having a very broad range of potential porosities (20% to 95%) while only describing the potential use of the carrier therein described as a drug-filled implant in only the most cursory manner. No examples of how such a carrier might actually be filled with a drug, or demonstrations of how effective it may be, are provided in the Smith reference. Ishii provides that direct methods of manufacturing porous carriers are only effective for making carriers of less than 50% porosity (see paragraph [0015]), while the greater porosity and control required for an effective drug release carrier can be provided only by the indirect method of saturating a polymer foam with ceramic slurry before burning the foam out and sintering the slurry (see paragraph [0014]).

Ishii actually teaches away from producing any article other than one having a tubular porosity, as it is stated in Ishii at ¶[0015] that articles produced by a method different to that of

saturating a polyurethane sponge with a ceramic slurry and firing exhibit only up to 50% porosity.

In addition the deficiencies of Smith and Ishii in teaching a porous ceramic carrier having a particular reticulated carrier porous configuration, as opposed to teaching or suggesting the totally interconnected pore network as claimed, and additionally in not teaching or suggesting the claimed pore sizes, is not remedied by the addition of Laurencin. Laurencin teaches a system for the controlled release of a substance which interacts with local cell populations at a physiological site. Such systems include the provision of bioerodable polymers such as PCPP-SA. Laurencin is not, however, concerned with the configuration of the pores of hydroxyapatite carriers and is therefore unable to provide teaching for taking a person having ordinary skill in the art from Ishii to the invention of claim 38. Since claims 39 - 42, 44, 45, 53 - 55, 59, 60, 62, 63, 72 and 73 are dependent on claim 38, these claim are also patentable over the combination of Smith, Ishii and Laurencin.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 103(a)

Claims 38-42, 44, 45, 53, 54, 56, 57, 59, 60, 62, 63, 72 and 73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (WO 98/15505), in view of Ishii (JP 04327525), further in view of Genin (US 6,767,550). This rejection is respectfully traversed.

The Examiner sets forth that Smith discloses porous ceramics infilled with drug substances for slow release (page 10, line 18 - page 11, line 3) and Ishii discloses sustained release medicine containing ceramic porous substances containing a biodegradable substance which contains the medicine, including anticancer agents, dispersed and held to the inner wall surfaces in pores and the outside surface of a ceramic porous substance.

The Examiner admits that Smith and Ishii do not specifically teach that the pores contain layers of medicament and degradable support, each layer being different from its neighbors, or alternating medicament-free and medicament-containing layers. However, the Examiner cites Genin, which allegedly discloses hydroxyapatite based bioresorbable materials incorporated with anti-cancer agents to form an implant used for treatment against cancer. The Examiner further argues that Genin teaches sustained release of the anti-cancer agents may be achieved after

implantation at the targeted sites, and that the dosage of the anticancer agent, the microstructure, morphology, and composition of the bioresorbable material allow control of the release profile (citing the abstract).

The Examiner further argues that it would have been further obvious to one having ordinary skill in the art at the time of the instant invention to provide the biodegradable support material which holds a medicament in the pores of the ceramic substance disclosed by Ishii in the form of alternating layers, and that one would have been motivated to do so, and would have had a reasonable expectation of success in doing so because each of Smith, Ishii and Genin are directed to the sustained release of a medicament from a hydroxyapatite-based implant for the treatment of bone tumor, and because Genin discloses that such multilayered structures are useful in implants for which the resorption rate is designed, or can provide benefits such as periodical release of anti-cancer agents.

However, the claims are patentable over the combination of Smith, Ishii and Genin for the following reasons. The claims are set forth above, and are not taught or suggested in the combination of Smith and Ishii. Smith provides a direct method of producing ceramic porous articles (i.e. the method produces the porous structure intrinsically, rather than relying on a ready-made porous support) having a very broad range of potential porosities (20% to 95%) while only describing the potential use of the carrier therein described as a drug-filled implant in only the most cursory manner. No examples of how such a carrier might actually be filled with a drug, or demonstrations of how effective it may be, are provided in the Smith reference. Ishii, in contrast, provides that direct methods of manufacturing porous carriers are only effective for making carriers of less than 50% porosity (see paragraph [0015]), while the greater porosity and control required for an effective drug release carrier can be provided only by the indirect method of saturating a polymer foam with ceramic slurry before burning the foam out and sintering the slurry (see paragraph [0014]). Ishii actually teaches away from producing any article other than one having a tubular porosity, as it is stated in Ishii at ¶[0015] that articles produced by a method different to that of saturating a polyurethane sponge with a ceramic slurry and firing exhibit only up to 50% porosity. The deficiencies of the combination of Smith and Ishii in suggesting a porous ceramic carrier having a particular reticulated carrier porous configuration, as opposed to

teaching or suggesting the totally interconnected pore network as claimed, and additionally in not teaching or suggesting the claimed pore sizes, is not remedied by the addition of Genin.

Genin teaches the use of granular or block hydroxyapatite implants, which may be porous or dense (column 6, line 35), for the delivery of anti-cancer agents. For instance, Genin describes a multilayered structure of pure and drug-loaded biomaterials for use as an implant for which the resorption rate is designed (see lines 19 to 21 of column 6).

However, Genin is concerned with ceramic implants in their green state – lines 66 to 67 of column 2 provide that the pressure used to form the implants ranges from 0.1 to 40 MPa, yet there is no description of any firing step. Indeed, the pores of the ceramic granules or discs described in Genin do not appear to be intrinsic in the structures of the articles, rather they are dependent on the presence of the drugs to be delivered in the pressing step (see Example 2 of column 8 of Genin).

Moreover, there is no disclosure of the overall density of the articles described in Genin. The pores of the present invention, which take the form of a network of coalesced spheres, could not be provided in a ceramic in its green state. This is because in applying the pressure necessary to form a green ceramic of some structural integrity, the bubbles which form the spherical pores would collapse.

Accordingly, Genin is not able to direct the skilled artisan from the drug-filled ceramic implants having tubular pores according to the combination of Smith and Ishii to the implants having pores made up of a network of coalesced spheres as required by the invention of claim 38.

It is therefore submitted that Claim 38 is inventive over Smith and Ishii in view of Genin. The Applicant further submits that claims 39 to 42, 44, 45, 53, 54, 59, 60, 62, 63, 65, 72 and 73 are, by virtue of their dependency on claim 38, inventive over Ishii in view of Genin.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

January 21, 2009

By 

Joseph F. Murphy
Registration No. 58,313
Customer No. 03000
(215) 567-2010
Attorneys for Applicants

Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.